

## REVIEW ARTICLE

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# Recent perspectives of management of breast cancer metastasis – an update

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### Summary

*Breast cancer is the leading cause of cancer related deaths in women and one of the most common cancers globally. The major obstacle in the management of breast cancer, especially at advanced stages, is metastasis. Metastasis in the advanced stages of breast cancer could decrease survival to approximately 5 years. The reasons could include lack of targeted receptors or chemotherapeutic agents for the management of advanced-stage breast cancer metastasis. The new emerging avenues for the management of this deadly pathological state include local manipulations like radiofrequen-*

*cy ablation (RFA), microwave thermotherapy, cryosurgery (cryotherapy), chemoembolization, radioembolization, breast surgery, or metastasectomy. Few single-institution reports showed improved survival in selected patients like those with oligometastatic stage IV breast cancer. The present review article focused on these emerging new multimodality treatment approaches for a possible efficient management.*

**Key words:** breast cancer, metastasis, multimodality, therapeutics

### Introduction

Metastatic breast cancer (mBC) is a research hotspot of various researchers working in the field of cancer therapeutics as mBC is very unlikely to be cured. Undoubtedly, there have been many improvements in survival with the newer systemic therapies, and the most probable targets in these therapies are HER-2, estrogen receptors (ER), progesterone receptors (PR), or both. Consequently, the practical application is limited to few patients only. Furthermore, the median overall survival (OS) still might change in a broad spectrum of cases. However, in triple negative breast cancer (TNBC) cases, months are required for effective response while HER-2 positive mBC cases take years for effective treatment response [1,2]. Recently metastasectomy has shown its potential in prolonging survival in colorectal metastatic cancer patients [3-5]. In the

last decade, the positive effects of metastasectomy were also confirmed in mBC patients [5]. Some of the positive observations with this therapeutic option included positive hormone receptor status, good response to chemotherapy, R0 resection and longer disease free survival (DFS) [6-8]. In the present review article, the main focus was mBC outcomes and the latest therapeutic avenues for effective management.

### Breast cancer metastasis to the liver and its management

One of the most common sites of breast cancer metastasis is the liver [9]. It is a well-known fact that patients with liver metastatic BC have short lifespan of just 1-2 years with systemic che-

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motherapy administration [10]. A recent review revealed positive effects of liver metastasectomy in mBC patients with median OS 40.5 months [9]. The most important prognostic factor, according to the investigators, was hormone receptor status positivity. Further, Thelen et al. also reported positive outcomes in 39 patients who underwent liver resection for mBC [11]. In addition, solitary metastasis was the most important prognostic factor in multivariate analyses [12]. So, it seems that hepatic resection in mBC is a quite obvious option for some of the patients. It has been estimated that 10-20% of patients are good candidates for surgical resection [12]. The other therapeutic options are discussed in later sections.

### Local ablative treatments for BC liver metastases

Local modalities like intra-arterial chemotherapy, radiation, and local ablative techniques are the therapeutic options for patients who are not good candidates for metastasectomy. In selected patients, these techniques, alone or in combination with other therapies might prolong the survival rate of patients with liver metastases.

### Percutaneous thermal ablation (PTA)

PTA is a local ablative treatment choice for oligometastases [13]. A small but selected population of mBC patients could be alive more than 5 years with this therapeutic intervention [14]. PTA methods include radiofrequency ablation, microwave ablation, or cryotherapy and are minimally invasive interventions leading to local necrosis around the tip of the needle. A recent study revealed positive effects of PTA in 79 mBC patients [19]. Lowest survival rates had been observed in patients who had extrahepatic metastases other than bone. PTA is a safe and effective treatment modality, particularly in selected patients. It could be used several times in large lesions and has a lower cost compared to other modalities.

#### *Cryotherapy and Laser-induced thermotherapy*

This is another option of local thermal ablation, which is different from PTA. It involves a probe tip that is maintained at  $-196^{\circ}\text{C}$  with liquid nitrogen in order to freeze the tumor [14]. A recent study showed positive outcomes of cryotherapy in combination with immunotherapy with highest OS of approximately 5 years [15]. However, there is paucity of information with regard to routine

usage of cryotherapy in mBC patients.

Laser-induced thermotherapy (LITT) uses laser energy and high temperature to induce irreversible necrosis in tumor tissue [15]. A study in the recent past (2004) reported on the application of laser-induced ablative therapies to treat mBC [16]. The authors treated 232 patients with 578 liver metastases by using MR-guided laser-induced interstitial thermotherapy and achieved a median OS of 4.3 years and 5-year survival rate of 41%.

#### *Chemoembolization and radioembolization*

Chemoembolization is a technique that involves reduction of the blood flow to liver by embolization of the hepatic artery, leading to ischemia. Under these conditions, chemotherapeutic agents, which are administered locally, result in prolonged drug exposure to the tumor [17]. However, overall response rate of chemoembolization is poor so far with maximum median OS of just 10 months [18,19], and, therefore, due to lack of positive literature with regard to use of chemoembolization for liver mBC, this method is not an option of choice for the management of breast cancer.

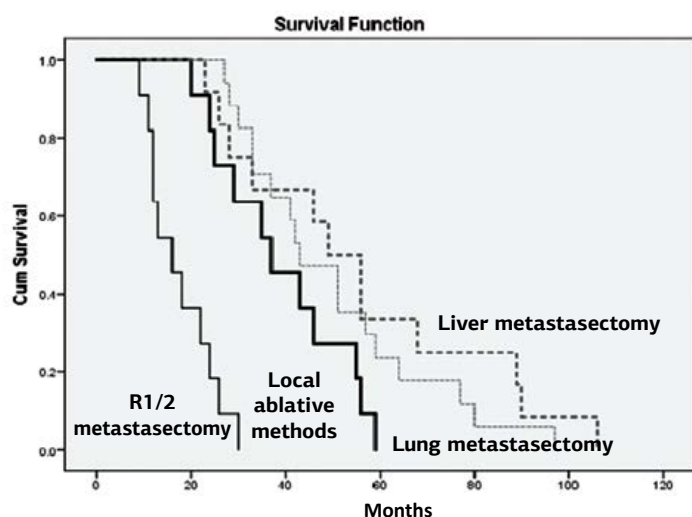
Radioembolization (RE) is a minimally invasive technique, which involves a combination of radiological interventional procedure with nuclear microspheres [18]. After the implantation into the tumor, the microspheres release a very high dose of radiation ( $>100\text{ Gy}$ ) with a tumoricidal effect as revealed in various earlier studies [19-22]. However, radioembolization showed an overall mixed therapeutic response.

#### *Stereotactic body radiotherapy (SBRT)*

SBRT is gaining popularity among BC patients with oligometastatic disease. It is an emerging, effective and safe treatment modality [23]. Median OS was 48 months and median progression-free survival (PFS) was 11 months, with actuarial OS rate at first and second year 93 and 66%, respectively. Milano et al. presented a study with 40 patients treated with SBRT with curative intent; only 14 of them had liver metastases. The whole study population had a 59% and 38% 4-year OS and PFS rate, respectively [24]. (Figure 1) shows the survival with surgery and local ablative methods.

## Breast cancer metastasis to the lung and its management

Lung is another common metastatic site



**Figure 1.** Overall survival with surgery and local ablative methods ( $p < 0.01$ ).

for BC especially common in HER2-positive and TNBC cases [25]. Surgical resection is one of the prime methods of choice for the management of metastasis to lungs and many studies have shown its positive outcomes. Meimarakis et al. assessed the median OS of 81 women after resection of pulmonary primary BC metastases [26]. Eighty-two percent of the patients had a R0 resection and achieved significantly longer OS compared to the R1-2 resection (103 vs 24 vs 20 months, respectively). Planchard et al. reported on 125 patients who had been treated with curative surgery of pulmonary mBC and they observed median OS 4.2 years in 58% of the cases [27]. In another study involving a large number of patients with lung metastatic BC, 84% of the patients had complete resection [28]. Lung metastasectomy should be considered especially in patients who had a long DFS, are oligometastatic and have positive hormone receptor status.

### Local ablative treatments for mBC to the lung

There is limited data available with regard of the use of local ablative methods against pulmonary metastases of breast cancer origin. Koelblinger et al. reported 22 cases of sarcoma lung metastases treated with radiofrequency ablation and showing 3-year OS rate in 85% of them [29]. Moreover, it is a well-tolerated, promising approach with improved outcomes [30,31].

Stereotactic body radiation therapy (SBRT) is a good option that does not involve resection. Milano et al. published the results of their prospective study that used curative-intent SBRT and included 121 patients, most of them diagnosed with mBC

and colorectal cancers. The authors showed that patients with BC had much better survival than other histologies [31]. PFS at 2 years was 36% for patients with BC compared with 13% for those with non-BC, and OS at 6 years was 47 vs 9%. Osti et al. presented 66 patients with 17% of them diagnosed with mBC and treated with SBRT [32]. The trial showed a significantly higher local control rate for lung, colon and BC metastases (Table 1).

### Breast cancer metastasis to the bone and its management

Palliative radiotherapy (RT) is an easily handled option for patients with metastatic bone disease. It is non-invasive and effective, but the main purpose of RT is to prevent skeletal-related events and to palliate pain [33]. Randomized trials and meta-analyses supported that there is a significant difference in pain relief between the single and multi-fraction RT for bone metastases [34-36]. A retrospective review of patients with metastases in one organ revealed that those with bone or thoracic lymph node metastases had better oncologic outcomes in comparison with those having solid organ metastases [35]. Moreover, SBRT performed on 393 patients included both BC metastases as well as other than BC metastases cases, and revealed positive outcomes, especially in patients who were previously irradiated [36]. So, the observed positive outcomes would encourage the use of SBRT as a prominent choice in the near future as it is practical and less toxic.

### Breast cancer metastasis to the brain and its management

Brain metastases are diagnosed in 10-20% of patients with breast cancer and if they are left untreated lead to a median survival duration of less than 2 months [37]. Pieper et al. presented their experience on 63 patients with BC brain metastases and observed median OS of 16 months with a 17% 5-year survival rate [38]. Ho et al. reported a large sample size study including 992 patients with either synchronous or metachronous brain metastases in BC patients and showed a median OS of 5 months after metastasectomy [39]. Metastasectomy is one of the treatment options for brain mBC. However, if there is contraindication of using RT, only then non-invasive or local ablation methods are used. A recent study with mBC comparing whole brain radiation (WBRT) with stereotactic radiosurgery (SRS), found that SRS

**Table 1.** Oncologic outcomes of the treatment modalities

<i>Authors, method</i>	<i>Number of patients</i>	<i>Surgery site</i>	<i>R0 rate, %</i>	<i>OS, months</i>	<i>5-year OS rate, %</i>	<i>Favorable prognostic factors</i>
<i>Surgery</i>						
Charalampoudis et al. (review)	1025	Liver	75	40.5	39	Hormone positivity, Good chemotherapy response, R0 resection, Late relapse
Groeschl et al.	115	Liver	86	52	27	Younger than 65 y, <5cm lesion
Abbot et al.	86	Liver	90	57	43.6	Estrogen positive, Good chemotherapy response
Hoffmann et al.	41	Liver	78	58	48	NA
Thelen et al.	39	Liver	72	74	42	Without previous metastasectomy
van Walsum et al.	32	Liver	90	55	37	Estrogen positive primary tumor
Bacalbasa et al.	43	Liver	91	32	58	Hormone positivity
Meimarakis et al.	81	Lung	81	103	52 (3 years)	R0, <3cm lesion, Hormone positivity
Chen et al.	41	Lung	-	-	51	<4 number of lesion
Planchard et al.	125	Lung			30	<2 cm lesion
Friedel et al.	467	Lung	84	36	38	R0 resection
<i>Local ablative modalities</i>					2/5 years	
Barral et al. Percutaneous thermal ablation	79	Liver, Bone, Lung	-	-	95/NA	NA
Melomi et al. Percutaneous thermal ablation	52	Liver		30	NA/27	<2.5 cm lesion
Jakobs et al. Percutaneous thermal ablation	43	Liver, None, Lung	-	60	NA	Bone metastases
Niu et al. Cryotherapy	91	Liver	-	83	NA	Immunotherapy with ablation
Mack et al. Laser-induced thermotherapy	232	Liver	-	52	NA/41	<4 metastases
Vohl et al. Chemoembolization	208	Liver	-	25	33 (3 years)	NA
Cianni et al. Radioembolization	52	Liver	-	11.5	NA	NA
Fendler et al. Radioembolization	81	Liver	-	8.7	NA	2 patients died during procedure
Scorsetti et al. Stereotactic body radiotherapy	33	Liver, Lung	53	48	66/NA	Chemotherapy
Milano et al. Stereotactic body radiotherapy	40	Liver, Lung	-	NA	38 (4 years)	
Wang et al. RF ablation	35	Lung	88	33	43 (3 years)	One lesion, <2 cm lesion
Bortolotto et al. RF ablation	523	Liver, Lung	-	35	NA	NA

OS: overall survival, RF: radiofrequency, NA: not applicable

patients had higher OS rates at 12 and 24 months compared to the WBRT patients [40].

### Surgery of primary tumor in metastatic breast cancer

Primary tumor resection in patients with mBC is also a rising trend in the management options of mBC. A recent study has proved that surgery of the primary tumor was advantageous as survival prolonged significantly in the resection group, especially in patients younger than 50 years with bone and soft tissue metastasis [41]. A SEER data analysis including 9734 stage IV BC patients, showed that median OS was significantly longer in the surgery group in comparison to the control group [42]. In another study with 208 patients the results were better in the surgery arm [43]. Furthermore, hormone receptor positive patients, HER2 (-) patients, younger than 55 years, and solitary bone metastasis were the favorable prognostic factors [44]. In

addition, a recent meta-analysis supported these findings, revealing a pooled hazard ratio of 0.63, signifying a 37% reduction in the risk of mortality in patients who underwent surgical resection of the primary tumor [45].

### Conclusions

From the data presented in this study it could be concluded that for the efficient management of breast cancer metastasis, the prime therapeutic modality of choice is surgery. Second option after surgery is SBRT, which has also revealed promising positive outcomes. On the other hand, RFA, cryotherapy, and Y90-based treatments are favorable options in special situations with comparable benefits.

### Conflict of interests

The authors declare no conflict of interests.

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